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CRITIQUE OF DRAFT CHEMICAL HAZARD INFORMATION PROFILE
on
MERCAPTOBENZOTHAZOLE DISULFIDE (MBTS)

Submitted to the
Environmental Protection Agency

by the
Chemical Manufacturers Association's
Rubber Additives Program Panel

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Introduction and Summary

The Chemical Manufacturers Association's Rubber Additives Program Panel has reviewed EPA's May 27, 1983, draft Chemical Hazard Information Profile (CHIP) on Mercaptobenzothiazole disulfide (MBTS). The Panel is concerned about the extensive reliance on Russian and East European abstracts and studies, many of which have not undergone appropriate scientific peer review. Since this document will be cited as a significant review of this chemical, more careful evaluation of the scientific data is warranted. Moreover, since the MBTS commercially produced in the U.S.S.R. may significantly differ in purity from the MBTS manufactured in the U.S., these Russian studies should be carefully scrutinized.

The CHIP was prepared from computerized literature searches that were initiated on December 28, 1982. The searches included general chemical, toxicological, environmental, commercial and regulatory data bases. Many of the studies are presented in the CHIP simply as a restatement of the abstracts obtained from the Chemical Abstracts Service. There appears to be little if any evaluation of the results. Moreover, there is no consistent effort to relate the results from different studies. This gives the appearance of a rushed, improperly evaluated presentation of the scientific data base for MBTS.

Though the disclaimer on the title page indicates that the report was not reviewed by either scientific or administrative branches of EPA, the stated purpose of the CHIP, i.e., to enable OTS to determine the level of concern and need for further assessment, cannot be accomplished if the data are not appropriately reviewed and presented.

Specific Comments on the MBTS CHIP

Specific comments on the draft CHIP are described below and presented by Section, page (pg) and paragraph (para) where possible:

Summary

para 2;

At least three statements are made without qualification and without supporting data:

"long-continued inhalation may cause lung inflammation and fibrogenicity...";

"MBTS puts stress on the nervous system..."; and,

"Functional reproductive disorders have been noted in women working with several compounds including MBTS".

The comment on lung inflammation is not clearly addressed in the text and fibrogenicity has not been demonstrated to be directly related to MBTS as the CHIP implies. The phrase "stress on the nervous system" is not only unsupported but conveys no real scientific meaning. Finally, any attribution of MBTS exposure to functional reproductive disorder in women is improper since there is insufficient evidence to determine whether the reported effects result from exposure to MBTS, other compounds or lifestyle factors. As presented in the CHIP Summary, these statements are inappropriate and will be open to misinterpretation.

Section 1

Pg. 1; No. 14;

Discussion of the release of SO_x from combustion of MBTS is misleading since combustion is not an expected fate of the chemical. Therefore, the release of oxides from combustion should not be included under chemical "reactivity".

Pg. 4; para 1;

Experience in industry does not justify a concern for the allergic potential of MBT and MBTS. In a study by Monsanto (unpublished report), testing of MBTS with human subjects did not demonstrate an irritation or sensitization response. Reports of allergic responses to rubber chemicals have been related primarily to reactions from body contact with finished rubber goods or responses of sensitive populations in chemical screening studies. The effects reported by Taft and Stroman should not be attributed to MBT or MBTS since these researchers failed to consider the effect of morpholine or of a morpholino-MBT accelerator which have been shown to be sensitizers in humans.

Pg. 4/5; para 3;

The CHIP is inconsistent in its treatment of the relationship of MBTS to MBT and other MBT-derived accelerators. The authors speculate on the potential worker exposure to MBTS based upon data for MBT. This approach supports further discussion in the CHIP of the toxicology of MBT in discussing the effects of MBTS.

Pg 6; para 3;

It is unclear from the CHIP how the projected total of 71,733 workers potentially exposed to MBTS is derived from the 775 workers presented in the table. In addition, the number of workers estimated is vastly different from estimates reported for other similarly used materials.

Pg. 7; para 1;

The Food and Drug Administration permits the use of MBTS in rubber articles intended for repeated or continuous contact with food (CFR 177.2600) and in adhesives (CFR 175.105). This conflicts with the cited statements of Heinisch (1974) which imply that MBTS is unsuitable for medical articles or products which come in contact with food.

Pg. 9; Table 1;

The LD50 value reported by Vaisman is not in agreement with all other acute data available. All commercial manufacturers of MBTS report oral LD50 values in excess of 5000 mg/kg. The CHIP acknowledges this inconsistency in the footnote presented on Pg. 9.

Pg. 10/11; para 1;

Reference to MBTS as an "equivocal tumorogenic agent" is another example of the lack of critical review inherent in the CHIP. NIOSH defines "equivocal" as "some evidence for tumorogenic activity." It is obvious from the review of the data presented that administration of MBTS to mice did not produce a statistically significant increase in tumors. While the document properly discusses the study, the use of the term "equivocal" in the opening sentence falsely gives the impression that a questionable but positive response has been reported. (Results of this study were discussed by Innes et al. [JNCI 1969] which should be cited as a reference.)

Pg. 11-13;

The discussions on mutagenicity and teratogenicity/reproductive effects are the most significant examples of improper and incomplete evaluation of results.

Mutagenicity

The effects for MBTS reported from Aleksandrov (1982) are essentially the same as those reported by Aleksandrov in 1974. These results are supported by findings from another Russian article by Mirkova. Aleksandrov also reported a weaker, but positive, response with MBT, the probable metabolite of MBTS, and positive responses were reported for two MBT-based sulfenamides. All of these results conflict with several recent studies many of which are reported in western literature. Hinderer (1981, 1982) reported the absence of mutagenic effects of a related sulfenamide (OBTS) in a series of in vitro assays and in a rodent dominant lethal assay. In addition, Hinderer et al. (1983) found mutagenic effects for MBTS in only one assay (mouse lymphoma) of a series of five in vitro mutagenicity assays. These results cast significant doubt on the accuracy of the data reported by Aleksandrov. The Panel is aware that the National Toxicology Program is in the process of finalizing a genotoxic study on MBTS.

Teratogenicity/Reproductive effects

As with the mutagenicity data, recent reports in scientifically peer reviewed journals raise serious questions about the validity of the Aleksandrov and Mirkova data. Hardin et al. (1981) reported the absence of teratogenic or embryotoxic effects following intraperitoneal administration of MBT on days 1 through 15 of gestation. Likewise, Stevens (1982) found no teratogenic effects in rats with a series of sulfenamides including those tested by Aleksandrov. These findings are further supported by Morita et al. (1981).

Pg. 13-14;

Several articles discussing the effects from exposure to various rubber chemicals are cited but are presented in a manner that is misleading to the reader. The CHIP implies that MBTS is the common link or most important compound contributing to the reported effects. Nevertheless, there is no evidence to conclude that the effects reported should be attributed to exposure to MBTS.

Pg. 14; para 2 and 3;

The statement that "MBTS toxicity is aggravated by pregnancy" (paragraph 2) is not supported by the data and fails to consider several important factors. The elevated levels in rats of serum glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase reported by Mirkova from exposure to 100 mg/kg of MBTS (paragraph 2) are in marked contrast to the results reported by Radeva (paragraph 3). Radeva reported a lowering of glutamic pyruvic transaminase and alkaline phosphatase following exposure to significantly higher doses of 400 and 800 mg/kg. There is no reason to suspect that pregnancy would cause an alternation of this type as a response to a chemical exposure. In addition, it is unclear as to whether the reported dosage was appropriately adjusted to account for increased maternal body weight as a result of fetal tissue development.

Pg. 14; para 3;

Considerable emphasis is given to the Stankevich study which is an evaluation of extracts from rubber materials, while minimal attention is given to the McCormick report which is a feeding study with MBTS.

SECTION II

Pg. 17; para 2;

See comment under Section I, Pg. 4/5; para 3.

Pg. 17; para 6;

Citation of the acute toxicity rating of Sax is in conflict with the generally indicated toxicity of this material. MBTS has an acute oral toxicity greater than 5000 mg/kg. The rating by Sax is inappropriate and should not be used to support a risk assessment.

Pg. 18; para 1;

Discussion of human health effects should be more clearly distinguished from adverse effects found in animal studies. Further clarification is needed since many of the reported studies involve multiple chemical exposures and are of limited quality.

Pg. 18; para 2;

Reference to workplace exposure levels exceeding an undefined "MAC" is inappropriate. It implies a workplace hazard without a discussion of the value for the MAC or the criteria used in setting the level.

Pg. 18; para 3;

As discussed under Section I, Pg. 10/11, para 1 reference to MBTS as an "equivocal carcinogenic agent" is inaccurate and inappropriate.

Pg. 18; para 6;

It is unclear whether the effects reported should be attributed to MBTS or other compounds.

Pg. 18; para 7;

See discussion under Section I, Pg. 6, para 3.

REFERENCES

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